Slow-Release Caffeine: A New Response to the Effects of a Limited Sleep Deprivation

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Study Objectives: The aim of this study is to assess the interest of the intake of a new galenic form of caffeine called " slow-release " caffeine (SR caffeine) during a decrease of vigilance due to a limited sleep deprivation.
Design: The controlled method used compared three doses of SR caffeine (150, 300 and 600 mg) with a placebo. Tests were performed 2, 9 and 13 hours after each treatment. Wakefulness level was assessed subjectively through questionnaires and analog visual scales, and objectively with the Multiple Sleep Latency Test. Performance level was also assessed regularly with an attention test, a grammatical reasoning test, a spatial recognition test, a mathematical processing test, a visual tracking test, a memory search test, and a dual task. The motor activity was evaluated by wrist actimeter and safety of treatment was observed by regular clinical examination.
Setting: NA
Participants: Twenty-four young and healthy volunteers (12 men and 12 women) participated in a 32-hour sleep deprivation.
Interventions: NA
Results: The results show a significant effect of slow-release caffeine vs. placebo, and on vigilance and performance when subjects became tired. The effects of SR caffeine lasted 13 hours after treatment. SR caffeine 300 and 600 mg are efficacious doses but the optimal dose (maximum effect without any side effects) for both men and women is after all 300 mg. Globally, there is no difference between placebo and caffeine during the recovery night period.
Conclusions: SR caffeine (300 mg) seems to be an efficient and safety substance to maintain a good level of vigilance and performance during limited sleep deprivation.
Key words: Sleep deprivation; wakefulness; cognitive performance; slow-release caffeine

INTRODUCTION

CAFFEINE IS ONE OF THE VERY COMMON COMPONENTS IN BEVERAGES. It is found in coffee, of course, but also in tea, chocolate-flavored products and cola-based beverages, etc.[1] Due to its behavioral and psychomotor stimulating properties, it is used to maintain vigilance, memory, and performance levels during limited sleep deprivation.[2-8] Some prolonged sleep deprivation and wake-sleep rhythm disruptions are common in everyday life, especially in emergency cases, during rescue operations, in the army, or during transmeridian flights. These situations lead to a certain number of vigilance and performance alterations, which in turn lead to a decrease in efficacy or to the onset of penalizing symptomatology.[9-12] However, the results obtained with the use of caffeine to increase vigilance and performance level vary greatly. Sometimes, the results are very positive; an increase in performance mainly in visual vigilance tasks[13] can be observed as well as an increase in the level of awakeness—measured by electrophysiological techniques [2]—for unusual situations such as night work. Other studies reported an absence of effects or heterogeneous results[14] and sometimes negative effects such as the onset of tolerance during repeated intake of caffeine[15] or the onset of anxiety with still relatively low doses (325 mg).[16] In a general way, all the studies selected from a bibliographic research report an unquestionable stimulating and awaking effect of caffeine, but the effect has a limited power—especially compared with amphetamine—and duration.[17,18] Moreover, repeated caffeine intake can lead to the onset of deleterious cardiovascular or neurological side effects when the dose exceeds 600 mg. Therefore, it seemed interesting to assess the effects of a new galenic form of caffeine called " slow-release " caffeine (SR caffeine) Stinergic®. The release of

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Table 1—Evolution of subjective evaluation of vigilance and mood evaluated by VAS (mean/sem) during sleep deprivation period in every experimental conditions: placebo, 150, 300, and 600 mg of SR caffeine (significant differences treatment vs. placebo are noted (*) in the table)

Items	Time	Placebo	Dose of caffeine		
			150 mg	300 mg	600 mg
awake/drowsy	T0 +2h	6.81±0.44	4.18±0.50*	3.98±0.51*	3.69±0.40*
	T0 +9h	7.03±0.52	5.24±0.50*	5.60±0.46	5.54±0.47
	T0 +13h	4.91±0.45	4.31±0.44	4.26±0.39	3.85±0.33
calm/excited	T0 +2h	2.92±0.44	3.44±0.54	3.73±0.49	4.71±0.49
	T0 +9h	2.50±0.33	3.21±0.45	3.06±0.44	3.71±0.55
	T0 +13h	4.03±0.50	3.50±0.47	4.33±0.51	4.50±0.56
strong/weak	T0 +2h	6.58±0.41	4.77±0.46	5.39±0.47	4.07±0.35
	T0 +9h	6.69±0.48	5.95±0.36	6.18±0.42	5.96±0.45
	T0 +13h	5.86±0.41	5.40±0.42	5.57±0.38	5.07±0.40
confused/clear ideas	T0 +2h	4.10±0.45	5.46±0.45	5.37±0.48	5.72±0.39
	T0 +9h	3.96±0.48	4.80±0.37	4.14±0.41	5.04±0.47
	T0 +13h	5.02±0.42	4.85±0.37	5.17±0.36	5.42±0.44
skilful/clumsy	T0 +2h	5.91±0.42	4.57±0.43	5.05±0.47	4.55±0.36*
	T0 +9h	6.03±0.43	5.41±0.41	6.02±0.39	5.46±0.45*
	T0 +13h	5.38±0.40	5.16±0.40	5.15±0.34	4.56±0.40*
nonchalant/peppy	T0 +2h	3.21±0.46	5.29±0.40*	4.80±0.32*	5.86±0.41*
	T0 +9h	3.21±0.36	4.05±0.31	3.85±0.40	4.34±0.43
	T0 +13h	4.45±0.35	4.53±0.44	4.65±0.38	5.33±0.34
pleased/unpleased	T0 +2h	4.51±0.42	3.53±0.31	3.62±0.46	3.00±0.36
	T0 +9h	4.28±0.42	4.10±0.39	4.17±0.45	4.13±0.43
	T0 +13h	3.02±0.45	2.49±0.29	2.26±0.43	2.38±0.37
worried/quiet	T0 +2h	6.66±0.42	7.13±0.38	6.98±0.48	7.01±0.37
	T0 +9h	6.98±0.32	6.95±0.38	7.03±0.39	6.57±0.36
	T0 +13h	7.21±0.34	7.37±0.33	7.36±0.36	6.92±0.37
slow witted/quick witted	T0 +2h	3.56±0.40	5.43±0.39*	5.69±0.36*	5.73±0.42*
	T0 +9h	3.60±0.38	4.08±0.33	3.69±0.42	4.12±0.37
	T0 +13h	4.20±0.36	5.15±0.34	4.72±0.40	5.47±0.35
tense/relaxed	T0 +2h	6.49±0.44	6.38±0.48	5.87±0.53	5.59±0.44
	T0 +9h	6.50±0.43	6.46±0.45	6.48±0.50	5.52±0.51
	T0 +13h	6.29±0.47	6.65±0.34	6.37±0.45	5.83±0.52
attentive/dreamy	T0 +2h	6.91±0.30	4.71±0.33*	4.84±0.35*	4.31±0.33*
	T0 +9h	6.90±0.34	6.62±0.35	5.76±0.39	5.56±0.45*
	T0 +13h	6.40±0.34	5.81±0.34	5.91±0.36	5.31±0.40
incapable/capable	T0 +2h	4.31±0.35	6.01±0.31*	5.48±0.47*	6.46±0.38*
	T0 +9h	5.09±0.40	5.33±0.32	4.88±0.44	5.26±0.39
	T0 +13h	5.37±0.42	5.45±0.41	5.80±0.37	5.54±0.35
happy/unhappy	T0 +2h	4.32±0.46	3.24±0.33	3.30±0.46*	2.83±0.35
	T0 +9h	4.27±0.51	3.57±0.38	3.44±0.39*	3.94±0.48
	T0 +13h	3.32±0.44	3.27±0.42	2.47±0.40*	3.01±0.41
antagonistic/amicable	T0 +2h	6.58±0.36	7.56±0.36	6.98±0.46	7.45±0.36
	T0 +9h	6.33±0.47	6.58±0.42	6.70±0.44	6.34±0.44
	T0 +13h	6.99±0.42	7.08±0.32	7.34±0.47	7.00±0.44
interested/bored	T0 +2h	5.53±0.31	3.74±0.37*	4.34±0.44*	3.39±0.47*
	T0 +9h	5.71±0.32	5.01±0.38	5.02±0.42	4.85±0.50
	T0 +13h	4.86±0.38	4.94±0.40	4.42±0.46	4.02±0.39
uncommunicative/sociable	T0 +2h	5.91±0.44	7.38±0.38	6.79±0.52	7.79±0.35
	T0 +9h	5.97±0.52	6.49±0.38	6.54±0.50	6.21±0.43
	T0 +13h	6.98±0.44	7.31±0.39	7.37±0.45	7.41±0.41

the active principle by SR caffeine makes it possible to reach plasmatic plateau within approximately four hours and to remain at this level for four to six hours. The specific pharmacokinetic characteristics of SR caffeine would allow to observe more prolonged pharmacodynamic effects connected with the doses. In this work we will evaluate the effects of three doses of SR caffeine vs. placebo in a group of male and female subjects.

METHODS

Subjects

Twenty four subjects: 12 men and 12 women (age range: 18–38; mean of 24 years) were recruited after a thorough clinical and biological examination. People with previous serious physical and mental disorders and alcohol or drug abuse were excluded from the study. Selected subjects did not consume high quantities of xanthic-based beverages on a regular basis (coffee, tea, and cola: equivalent to no more than three cups a day) nor smoke more than five cigarettes a day. Finally, they had not taken part in any other drug test within the three months preceeding the present study. The subjects committed themselves to not drinking alcohol or caffeine-containing beverages during each experimental session. The study was carried out in compliance with Helsinki agreements. The subjects were informed of the objectives and of the conditions of the experiment and gave their written informed consent after having been included in the study which had been approved by the Aulnay-Sous-Bois Ethical Committee (France).

Design and Treatment

The controlled method used compared three doses of SR caffeine (150, 300, and 600 mg) with a placebo. Each subject received every treatment in four double-blind situations separated by one week of wash-out. The subjects received the four treatments according to a randomized order.

Procedure

The subjects took part in a psychomotor test training session before starting the experiment in order to obtain a steady performance. During this session, the subjects also filled in a Horne and Ostberg questionnaire to characterize their sleep.[19] The experimental sessions as such were arranged one week after the training session for each subject.

The subjects arrived at 06:00 in the morning after having had a breakfast without tea or coffee. They spent the day, the night and the following day until 05:00 PM on the experimentation premises. They were placed under surveil-

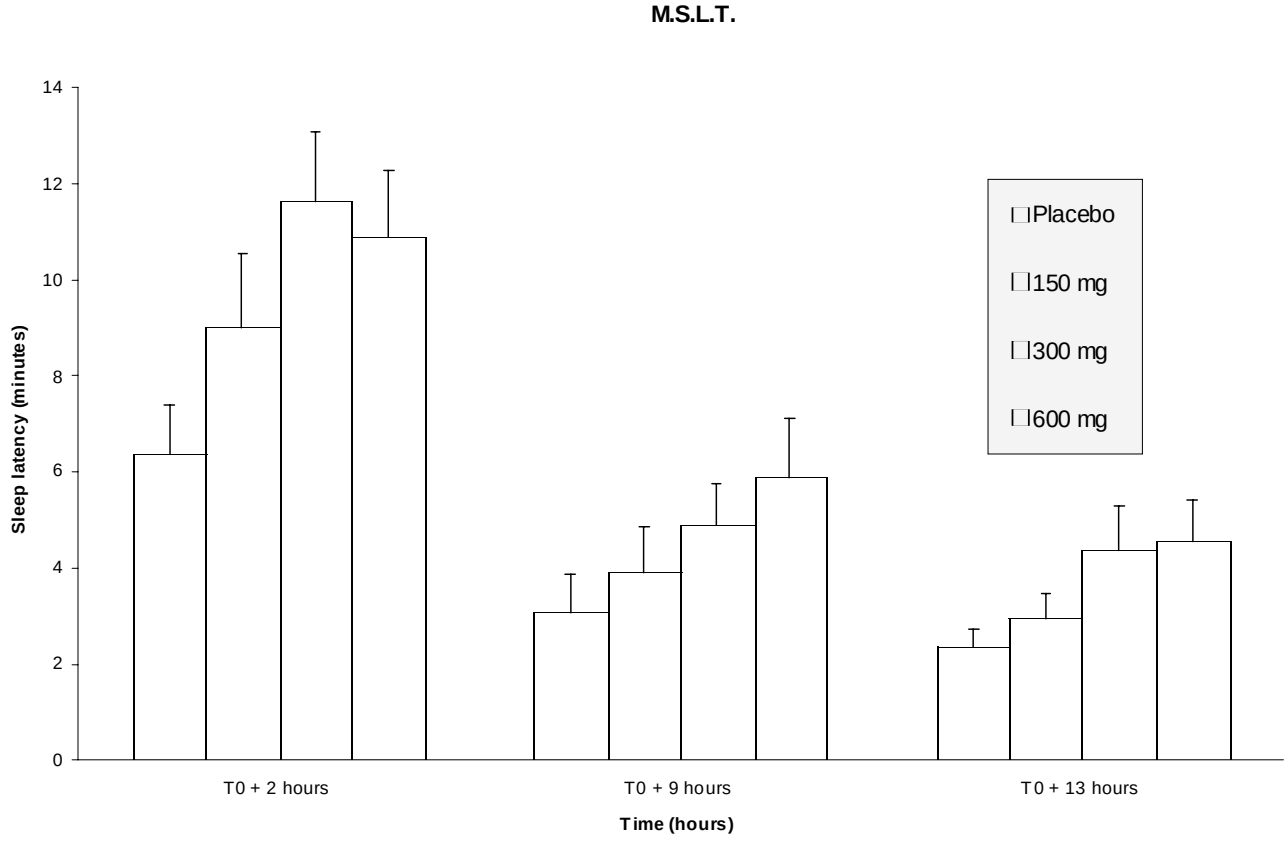

Figure 1—Evolution of the sleep latencies (mean/sem) during sleep deprivation period during placebo and SR caffeine 150, 300 and 600 mg experimental conditions, 2, 9, and 13 hours after time of drug intake (T0). 1, 2, 3, 4: significant effect compared with placebo, 150 mg, 300 mg, and 600 mg situations, respectively.

lance to keep them awake and to insure that they were subjected to a real 32-hour sleep loss. The treatment was administered at midnight (H0). Tests were performed 2, 9, 13 hours after the treatment, (i.e. after 20 hours, 29 hours, and 33 hours of wakefulness).

Evaluation of Wakefulness

Wakefulness level was assessed objectively by repeated measurements of the Multiple Sleep Latency Test (MSLT) visually read[20] and with an analysis of EEG signal obtained during MSLT test.[9] This EEG analysis was carried out with the MORPHEE system which processed—with digital filters—the data coming from two EOG bands, one EMG band, and one EEG band. Electrodes were located so as to provide differential recordings from two EEG channels (C3-C4 and O1-O2): an EOG channel and an EMG channel.[21] The sleep stage was deduced and the hypnogram was obtained according to logical, combinatory, arithmetical, and sequential criteria imposed by Rechtshaffen and Kales' rules.[22] One of the main analyses was based on the ratio of certain EEG frequencies based on a bandpass filtering.[23] The system considered as an activity area the most common frequency band. The components of minor frequencies that could exist were ignored; the system worked on an exclusive basis.

Wrist actigraphy was also used as an objective but indirect criteria of alertness as described and validated by several authors to measure of sleep/wake activity.[24-26] The number of movements was measured at every time they occured. The subjective aspects were evaluated by Bond and Lader visual analog scales (VAS).[27]

Evaluation of Performance

Performance level was evaluated by six psychomotor tests from the STRES test battery (Standardized Tests for Research with Environmental Stressors) designed by a work group of the Aeromedical commission of the AGARD (Advisory Group for Aerospace Research and Development - [OTAN]).[12] These tests—selected from among the most commonly used tests which met validity, reliability, and sensitiveness conditions—were implemented on microcomputers. The first test was a mathematical processing task with research of information in long-term memory and sequential treatment in short-term memory, also named working memory. The second test was a memory search task and included the following steps: detection and recognition of a target stimulus; research in memory and comparison; selection of the response. The third test consisted of a spatial processing task measuring the short-term visual memory performance. The fourth test was a visual tracking test aimed at measuring the resources used to perform a continuous manual control task. The fifth test was a grammatical reasoning test measuring the skills to handle grammatical data using working memory. Finally, the sixth test was a dual task simultaneously involving a visual tracking task and a memory search test and making it possible to measure divided attention abilities.[28] Attention level was measured by a symbol cancellation test.[29]

All these tests were used previously during sleep deprivation experiments and were found sensitive to sleep loss.[21]

Tolerance Evaluation

Tolerance was evaluated by spontaneous complaints from the subjects. During the whole session, a regular clinical examination of the subjects, including arterial pressure and heart rate recording with an automatic tensiometer on seated subjects, was realized. All subjects were given a questionnaire about the quality of the night following the tests. A full blood test was performed before and after experimental sessions.

Statistical Analysis

The different criteria were separately analyzed by ANOVA (PCSM 6.2 - DELTASOFT, France) with repeated measures—either for the analog visual scales, for the attention test, for the different tests of the AGARD STRES Battery, or for the MSLT test. These repeated measures analyses with three factors: treatment (SR caffeine 150, 300, 600 mg and placebo), sex (male - female) and time with three levels (2 hours, 9 hours, and 13 hours after treatment) were followed by a Newman-Keuls test when variance analysis showed significant effects between groups. A $p<0.05$ was used for statistical significance.

Table 2—Repartition of the ratio of EEG frequency bands during MSLT measures in every experimental conditions: placebo, 150, 300, and 600 mg of SR caffeine (significant differences treatment versus placebo are noted (*) in the table)

Treatment	EEG frequency band		
	θ	α	β
Placebo	76.6	18.6	4.6
SR Caffeine 150 mg	70.2	22.5	7.2
SR Caffeine 300 mg	69.8*	22.6*	7.5
SR Caffeine 600 mg	64.6	27.7	7.6

RESULTS

The population studied is made up of young, healthy men and women. The mean weight was 75 kg for men and 58 kg for women.

As far as sleep hygiene is concerned, interpreting Horne and Ostberg's questionnaire reveals that a wide majority of the subjects did not show any particular morning or evening preference (18 out of 24) and that only three subjects preferred mornings whereas the last three subjects preferred evenings. The mean duration of sleep (eight hours) as well as the other qualitative sleep parameters were consistent with the results usually obtained for a population of young adults.

Wakefulness Aspect

Measurement of sleep latencies is a test that is sensitive to sleep deprivation. Sleep latencies decrease significatively when sleep deprivation increases ($F_{2,44}$=46.49 ; p<.0001) but they are longer when the effects of caffeine treatment are observed than with placebo. An increase in latencies can be observed according to the dose of caffeine ($F_{3,66}$=5.52; p<.002), which is particularly significant for a 300 mg dose of caffeine evaluated at T0 + 2 hours (Figure 1). A certain number of subjects did not fall asleep during the test (20 minutes). It appears that all of them fell asleep in a placebo condition and that the number of subjects who did not fall asleep was higher for the T0 + 2 hours session than for other sessions, whatever the dose of caffeine administered (150, 300, and 600 mg), and that women are more sensitive to the action of caffeine than men.

As far as VAS are concerned, no significant effect of caffeine treatment can be observed for the following items: Incapable/Capable, Worried/Quiet, Tense/Relaxed, Antagonistic/Amicable.

However, there is a significant positive effect of caffeine intake vs. placebo for all the following items: Awake/Drowsy ($F_{3,66}$=9.23; p<.0001), Confused/Clear ideas ($F_{3,66}$=3.93; p=.012), Strong/Weak ($F_{3,66}$=6.32; p=.001), Nonchalant/Peppy ($F_{3,66}$=7.50 ; p<.0001), Slow-witted/Quick-witted ($F_{3,66}$= 8.39 ; p<.0001), Attentive/Dreamy ($F_{3,66}$=11.83 ; p<.0001), Interested/Bored ($F_{3,66}$=4.79; p<.0001), Calm/Excited ($F_{3,66}$=4.80; p=.004), Skillful/Clumsy ($F_{3,66}$=3.93;p=.012), Happy/Unhappy ($F_{3,66}$=3.77 ; p=.014), Pleased/Unpleased ($F_{3,66}$=2.94; p=.038), and Uncommunicative/Sociable ($F_{3,66}$=3.38 ; p=.022).

The subjects felt particularly less drowsy and less dreamy, had clearer ideas, and were more quick-witted; they were peppier and more skillful and felt stronger after having taken caffeine, than with placebo.

A more thorough analysis of these results makes it possible to obtain more accurate conclusions about the duration of the effects of caffeine and to assess which dose is the most effective. All these results are described in the Table 1.

It appears that—for the three doses of caffeine—these positive effects were very significant from the first evaluation (two hours after treatment) for the following items: awake, peppy, attentive, capable, quick-witted, and inter-

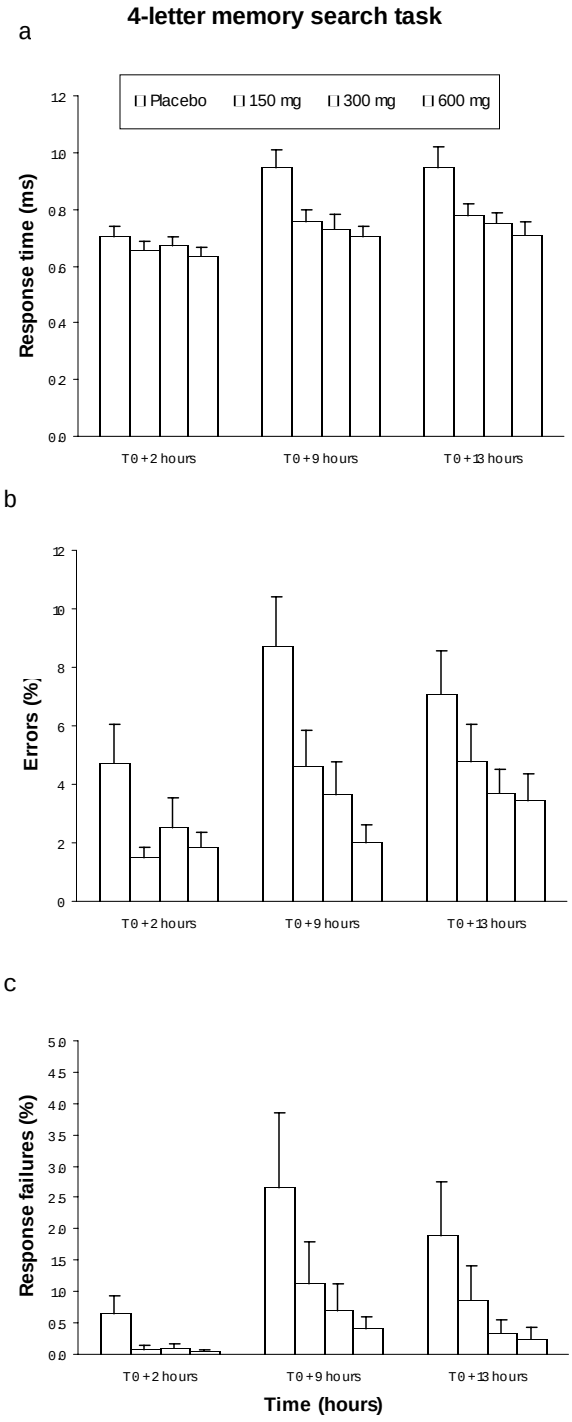

Figure 2 a, b, c—Evolution of performance during sleep deprivation period in memory search task with 4 letters, for reaction times (a), percentage of errors (b), and number of response failures (c) in every experimental conditions: placebo, 150, 300, and 600 mg of SR caffeine, 2, 9, and 13 hours after time of drug intake (T0). 1, 2, 3, 4: significant effect compared with placebo, 150 mg, 300 mg, and 600 mg situations, respectively.

ested. The effect was still significant nine hours after treatment for the " awake " item with a 150 mg dose and for the "attentive" item with a 600 mg dose. No significant effect could be observed 13 hours after treatment.

For a certain number of items, a significant effect of the gender factor was observed. This difference between men and women from the subjective point of view mainly applies to the criteria related to the levels of wakefulness or performance and less to the mood criteria. The following criteria were concerned: awake/drowsy, skillful/clumsy, nonchalant/peppy, strong/weak, confused/clear ideas, slow-witted/quick-witted, incapable/capable on the one hand and pleased/unpleased on the other hand. No difference was observed for the following mood criteria: calm/excited, worried/quiet, tense/relaxed, attentive/dreamy, happy/unhappy, hostile/friendly, interested/bored, and uncommunicative/sociable.

The comparison of global actimetry data between the different situations (placebo, 150, 300, and 600 mg of SR caffeine) does not show any statistical difference.

An analysis of the EEG signal obtained during sleep latency recordings was carried out according to frequency bands. For each subject, four experimental conditions were compared: 1) placebo, 2)150 mg of S.R. caffeine, 3)300 mg of SR caffeine, and 4)600 mg of SR caffeine.

This study is based on the digital analysis of frequency band by time slot. The frequency bands are dependent: theta + alpha + beta = 100%. The delta band is not represented in our study. The synthesis of the global dose results is shown in the Table 2.

There is a significant effect of the " treatment " factor for the alpha ($F_{3,66}$=3.16; p=.029) and theta ($F_{3,66}$=3.68; p=.016) frequency bands. The higher the dose of caffeine administered, the lower the percentage of theta waves compared with all the waves observed during recordings. This difference is significant between the 300 mg dose of caffeine and placebo. Moreover, an effect of the " time " factor can be observed for the theta ($F_{2,44}$=3.37; p=.042) and beta ($F_{2,44}$=6.22; p=.004) frequency bands. Finally, there is no difference between men and women.

Recovery Period

The study of the whole population questionnaires makes it possible to show an increase in the mean sleep time after sleep deprivation. Moreover, the recovery night is always longer in placebo condition vs. caffeine treatment. During recovery sleep, no big differences can be observed in the number of times the subjects awoke at night after caffeine treatment or in placebo condition. Sleep latencies during recovery nights were globally shorter than that of the baseline. However, no significant difference was observed between placebo condition and caffeine treatments. The subjects went to bed much earlier during the recovery night than during the reference night. The number of subjects who went to bed before 11:00 PM was higher for the placebo population than for the population treated with caffeine. The subjects of the placebo population also tended to get up later than the subjects treated with caffeine. The difference is mainly due to the male population. Moreover, getting up early did not seem to be more difficult under treatment than under placebo. Sleep quality appeared to be lower during the recovery night than during the reference night but no difference was shown between placebo condition and caffeine treatment. The subjects dreamt less during the recovery night than during the reference night and less with a 300 mg or a 600 mg caffeine treatment than under placebo.

Performance Aspect

No statistically significant difference was shown in the attention test between SR caffeine treatment and placebo. However, a global significant effect of the " time " factor

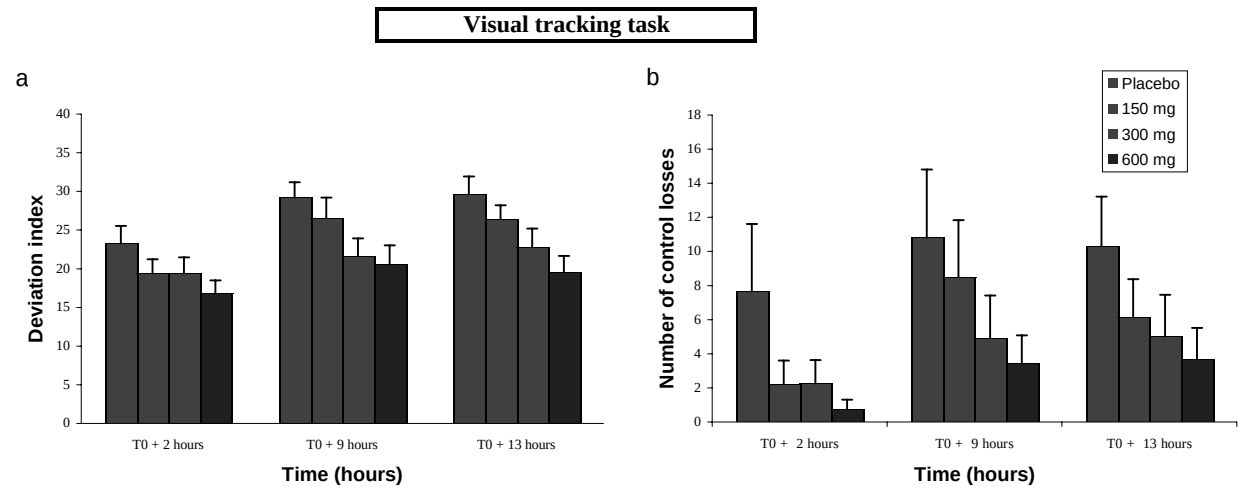

Figure 3 a, b—Evolution of performance during sleep deprivation period in visual tracking task for deviation index (a) and number of control losses (b) in every experimental conditions: placebo, 150, 300 and 600 mg of SR caffeine 2, 9, and 13 hours after time of drug intake (T0). 1, 2, 3, 4: significant effect compared with placebo, 150 mg, 300 mg, and 600 mg situations, respectively.

(F2,44=54.26; p<.0001) was observed for both of the criteria measured, the attention performance was significantly diminished at 02:00 AM compared to the other two test sessions.

For the STRES Battery three response criteria were taken into account for the mathematical processing, the spatial recognition, the grammatical reasoning, and the memory search tests: 1)the mean response time for correct responses, the percentage of errors; and 3)the response failure rate within the time given for the test. For tracking tasks—alone or during a dual task—two criteria were taken into account: the deviation index of a mobile cursor from the center of the target; and 2)the number of cursor control losses (i.e. the number of times the cursor went completely off the screen).

Globally, there was a significant " treatment " effect on numerous response criteria. In the grammatical reasoning task the subjects responded more rapidly with a 300 mg or a 600 mg dose of caffeine than with placebo ($F_{3,66}$=7.90; p<.0001), this effect was the same for the percentage of errors ($F_{3,66}$=3.62; p=.017) and the number of response failures ($F_{3,66}$=4.05; p=.001). In the spatial processing task the subjects made less errors with a 600 mg dose of caffeine than with placebo ($F_{3,60}$=5.74; p=.001). In the two-letter memory search task the subjects responded more rapidly with 150 mg, 300 mg, and 600 mg doses of caffeine than with placebo ($F_{3,66}$=11.37; p<.0001); the same effect was observed for the percentage of errors ($F_{3,66}$=2.91 ; p=.04) and in four-letter memory search task (Fig. 2 a, b, c) the subjects responded more rapidly), and made fewer errors ($F_{3,66}$=10.36; p<.0001) with 150 mg, 300 mg, and 600 mg doses of caffeine than with placebo; a same effect was observed for the number of response failures ($F_{3,66}$=5.50; p=.002). In the visual tracking test (Fig. 3 a, b) the subjects had a lower deviation index (higher performance) with 300 or 600 mg of caffeine than with placebo ($F_{3,66}$=11.76 ; p<.0001) and a higher deviation index with 150 mg than with 600 mg of caffeine; their number of control losses was also lower with 300 mg and 600 mg of caffeine than with placebo ($F_{3,66}$=4.93 ; p=.004). Finally, for dual task, in the tracking with concurrent two-letter memory search task, the subjects had a lower deviation index with 300 mg or 600 mg of caffeine than with placebo and with 600 mg compared with a 150 mg dose of caffeine ($F_{3,66}$=9.51; p<.0001); in the tracking with concurrent four-letter memory search task the number of control losses the subjects had a lower deviation index with 150, 300, or 600 mg of caffeine than with placebo and with 600 mg compared with a 150 mg dose of caffeine ($F_{3,66}$=11.31; p<.0001); moreover, fewer control losses were observed with 150, 300 or 600 mg of caffeine than with placebo ($F_{3,66}$=3.98; p=.023); in the 2-letter memory search task; this effect was observed for response time ($F_{3,66}$=9.91; p<.0001), number of errors ($F_{3,66}$=5.35; p=.002); number of response failures ($F_{3,66}$=3.36; p=.023), the subjects responded more rapidly with 300 or 600 mg of caffeine than with placebo and with 600 mg compared with a 150 mg dose of caffeine; number of errors and response failures were higher under placebo than with 600 mg of caffeine and in the four-letter memory search task the subjects responded more rapidly with 150, 300, or 600 mg of caffeine than with placebo and with 600 mg compared with a 150 mg dose of caffeine ($F_{3,66}$=10.97; p<.0001); the number of errors was higher under placebo than with 300 or 600 mg of caffeine ($F_{3,66}$=6.23; p=.001), and the number of response failure was higher under placebo than with 150, 300, or 600 mg of caffeine ($F_{3,66}$=4.37; p=.007). No significant difference was observed between caffeine and placebo conditions for the mathematical processing task.

A more detailed analysis of the results makes it possible to determine the most effective dose of caffeine to maintain performance on the one hand, as well as the required conditions for the effects of SR caffeine to last on the other hand. As is the case for the wakefulness aspects, there is a "dose " effect characterized by an increasing number of statistically significant differences between caffeine and placebo conditions as the dose of caffeine administered is increased.

However, as far as the duration of SR caffeine action is concerned, the effects observed were very different from those described for wakefulness. As a matter of fact, there was no significant difference for the first series of measures two hours after the treatment was administered. The highest number of significant differences between caffeine and placebo was observed during the second experimental session (i.e. nine hours after the treatment was administered). Performance was higher with caffeine—whatever the dose - than with placebo, as far as the number of errors in the spatial processing task, the response time to two- and four-letter memory search task, and the number of errors for the four-letter memory search task are concerned. With the 300 and 600 mg doses of caffeine, the subjects also made fewer errors during the four-letter memory search task performed during the dual task. Finally, with the 600 mg dose only, they did less errors during the two-letter memory search task; the deviation index was better for the tracking task performed either alone or within the frame of the dual task with two or four letters. Lastly, the response times were shorter for the two- and four-letter memory search tasks performed within the frame of the dual task. During the last experimental session (i.e., 13 hours after treatment), SR caffeine still had a certain efficacy on performance for memory search tasks and tracking tasks performed either alone or in the frame of the dual task with 150, 300, and especially 600 mg of caffeine.

There was small difference between men and women. Only the following criteria were significantly different:

percentage of errors for the grammatical reasoning test, number of response failures for the spatial processing task and deviation index for the tracking task with two letters during the dual task. For every treatment, placebo and SR caffeine 150, 300, 600 mg, men performance was better than women performance. For men as women, SR caffeine improved performance compared to placebo. A separate study of the male / female populations revealed that women were more sensitive to the effects of caffeine to maintain wakefulness from the lowest dose whereas for men, the most obvious effects were observed with 300 mg and especially with 600 mg of caffeine.

Significant interactions were observed between the "treatment" and "time" factors for the response time during the mathematical processing task, the four-letter memory search task alone and during the dual task as well as for the number of errors during the four-letter memory search task of the dual task and for the number of response failures during the two-letter memory search task of the dual task. These significant interactions show that the influence of the ultradian rhythm is maintained in these conditions.

Tolerance Aspect

Clinical tolerance—in the experimental conditions—was excellent for 16 subjects out of 24. Eight subjects (seven females) suffered minor intercurrent disorders: numbness, shaking, muscular pains, palpitations, and/or headaches. These symptoms remitted spontaneously and did not prevent the study from being continued. Two clinically annoying events occurred after placebo administration and should be related to undetermined external factors or to sleep deprivation. No biological abnormality possibly related to caffeine was observed.

DISCUSSION

Although all the tests did not show an univocal response to treatment, it can be said that—whatever the dose administered—SR caffeine increases the objective and subjective level of wakefulness, as well as performance compared with placebo for the experimental conditions of sleep deprivation.

In a general way, all the doses are active. However, the 300 mg dose is globally the most effective dose at T0+2 hours.

Duration of efficacy is variable and should be studied as a function of the dose, test, and population. Globally for example: for 150mg of caffeine, a positive effect was observed for eight items of the analog visual scales at T0+2 hours, for a single item (awake/drowsy) as well as for the spatial processing test and the memory search test at T0+9 hours, and for the memory search test and the tracking test at T0+13 hours. For 300 mg of caffeine, a positive effect was observed for seven items of the analog visual scales and for the MSLT at T0+2 hours, for the spatial processing test, for the memory search test, and for the tracking test at T0+9 hours and for the memory search test and the tracking test at T0+13 hours. Finally, for 600 mg of caffeine, a positive effect was observed for eight items of the analog visual scales at T0+2 hours, for a single item (attentive/dreamy) as well as for the spatial processing test, the memory search test and the tracking test at T0+9 hours, and for the memory search test, the tracking test and the dual task at T0+13 hours.

Therefore, it appears that the quickest subjective (VAS) and objective (MSLT) efficacy was obtained with a 300 mg of caffeine. However, repercussions on psychomotor performance appeared much later. Compared with placebo conditions, the decrease in the number of response failures for the memory search and grammatical reasoning tasks, as well as in the number of control losses for tracking tests, can be considered as an indication that vigilance is maintained in spite of sleep deprivation (" Walter Reed hypothesis ").[12,30] This confirms the wakening effect of caffeine. It should also be noted that the action of caffeine is not limited to shorter response times but that it also has a positive effect on the number of errors. As a matter of fact, caffeine seems to have a global action on information processing.

The delayed effect of caffeine intake can be explained by the late degradation of psychomotor performance compared with the subjective aspect which is more rapidly vulnerable as shown by the results obtained in placebo conditions. As a matter of fact, caffeine acts as a stimulating substance when there is no sleep deprivation[14,31,32] but is mainly active when there is a previous degradation of performance.[11,33] It is also more active in non-smokers who are low coffee users than in smokers who are heavy coffee users.[13] The interest of a new galenic form of caffeine is the delayed effect due to the slow release of caffeine granules. Most of the studies carried out assessed the effect of caffeine 45 to 50 minutes after administration,[34] three and six hours after,[35] one hour after,[33] 40 minutes and three hours after treatment,[36] that is close to treatment administration, which corresponds to the plasmatic peak of caffeine. The original feature of the results obtained in the present study is the persisting significant effect of caffeine nine hours, and for certain tests 13 hours, after administration. Moreover, a " dose " effect of SR caffeine was observed since the number of tests which were sensitive to the effect of caffeine increased with higher doses. This effect was reported in the literature: caffeine administration at a 200 mg dose, or less, does not induce any effect or induces little effect[37] whereas 250 mg and 400 mg doses induce stronger and more constant effects.[4,38]

The tests implemented in this study were also used by most of the authors to assess the impact of a psychotrope on vigilance and performance in human. The Multiple Sleep Latency Test , which is widely used, gives a good index of

the wakening effect of a substance with or without sleep deprivation[4,38] which explains the effect observed with SR caffeine from the second hour after treatment. A quantified analysis of the electroencephalographic signal when caffeine was administered showed an increase in the global power of the signal. This is due to an increase in alpha- and beta-frequency waves in the EEG[11,14] whereas a decrease in the alpha/beta ratio was observed in sleep deprivation conditions without caffeine.[9] The results obtained with SR caffeine are therefore consistent with those related to caffeine in the literature.

Measuring motor activity of the subjects with a wrist actimeter is aimed at assessing the motor component of the stimulating effect of caffeine.[39] In the present study, no globally significant difference was shown—thus confirming the inocuity of the dose administered.

The absence of significant results for the attention test (symbol cancellation test) and the thorough analysis of the data obtained required the following detailed study. A sensitive test was implemented, assessing a subject's attention abilities which evolve during the 24-hour period. This circadian fluctuation was also observed in our study since a significant effect of the " time " factor was shown on the number of correct answers and on the accuracy index. The absence of a statistically significant difference between placebo and SR caffeine treatment stems rather from the absence of an extensive degradation under placebo conditions and, consequently, from the low improvement in performance after caffeine administration.

The results obtained for the psychomotor tests confirm the efficacy of SR caffeine to maintain a good level of performance despite the negative effects of sleep deprivation. The effect of caffeine consumption on performance leads to much debated results. In normal conditions and according to the dose, caffeine may or may not improve recollection in memory tasks;[40,41] caffeine decreases performance for tasks requiring a fine motor coordination, increases anxiety and the feeling of tension,[42] and improves the choice reaction time as well as the results of a tracking task and the response time for a short-term memory task.[31] Caffeine also induces an increase in performance for visual vigilance task.[13] However, the results are more constant in fatigue or sleep deprivation conditions. Therefore, caffeine was tested to maintain performance during continuous operations with sleep deprivation. For Walsh et al.[2] caffeine consumption (200 mg) at the beginning of night work increases objective wakefulness over eight hours of work and maintains vigilance to baseline for the mathematical, logical reasoning, and visual vigilance tests during the whole experiment; whereas a degradation was observed for the placebo group. During a 64.5 hour sleep deprivation, a 600 mg dose of caffeine taken after 49 hours of wakefulness improves performance for reaction time, calculation, and logical reasoning tasks for 12 hours after administration.[43] For Fagan et al.[44] the facilitating effects found in caffeine could be related to the fact that caffeine fights against the degradations of perfomances caused by fatigue. This hypothesis was confirmed by Lorist et al.[6] tired subjects showed a higher increase in performance (decrease in error rates) after caffeine administration than rested subjects.

The sleep length of recovery sleep observed in placebo group is consistent with previous observations.[45,46] After sleep deprivation, as long ago as one night, the spontaneous sleep time during the first recovery night increases compared with reference night. Administration of SR caffeine does not seem to involve important differences concerning these aspects of recovery sleep. No recent litterature data were found about sleep recovery and caffeine.

Few studies provide data on the action mechanism of caffeine. It is probably complex and depends on the properties of the caffeine considered: antagonist action of receptors to adenosine as far as the decrease in slow waves of the EEG are concerned,[47] action on adenosine A1 receptors to increased neuronal discharge and synaptic transmissions, therefore facilitating caffeine-related convulsive attacks; or effects on the cholinergic system in the case of an increase in cognitive properties[48] or in the case of the antagonism of the debilitating effects of alcohol.[31] Globally, caffeine could increase cortical wakefulness and perceptive sensitivity without affecting central processes.[6] However, caffeine could modify interhemispheric distribution of neurotransmitters which the turnover would be modified by competitive blocking of receptors to adenosine.[49]

Apart from these beneficial effects, some well-known side effects can be observed. In general, for doses over 600 mg, the effects are mainly cardiovascular or neurological;[17] however, tolerance can appear for lower doses and with repeated administrations.[15] Anxiety was also described in some subjects.[16] In our study, the " worried " and " tense " items of the VAS under caffeine were not significantly different from placebo.

All the results obtained in the study show essentially the prolonged effect of SR caffeine on vigilance and performance data, without major side effects. These results contrast with those generally found with caffeine solution where the pharmacodynamic effects are limited in duration[50] and where doses higher than 400 mg induce severe side effects.[51]

Another effect observed in our study was a higher sensitivity of female subjects to the effects of SR caffeine, especially from the subjective point of view. It was also in the female population that some behavioral (shivering) or cardiovascular (tachycardia) disorders were observed for the highest dose of caffeine (600 mg). Moreover, SR caffeine efficacy was observed for lower doses in female, than in male, subjects and lasted longer. These differences are mainly due to two factors: a generally lower weight of female subjects where the dose administered is the same

and women were taking oral contraceptives. Besides, females subjects appeared to be more sensitive than men to sleep deprivation and SR caffeine is more effective with a higher decrease in vigilance caused by sleep deprivation. As a matter of fact, the studies carried out so far, with caffeine or with SR caffeine, did not show any stimulating effect without sleep deprivation conditions.[52] The difference in sensitivity according to sex was sometimes reported in the literature but with contradictory results. Caffeine increases the subjective effort required for a visual vigilance task in female subjects (whereas it is decreased in males).[33] With a single 325 mg dose of caffeine, male subjects become more anxious than female subjects.[16] However, strangely enough, most of the studies including male and female subjects did not compare the two populations.[15,37]

As a conclusion, SR caffeine seems to act as a vigilance regulator and according to the dose administered, would tend to correct more or less the effects of sleep deprivation. Therefore, SR caffeine indications could be all the situations requiring a good quality of wakefulness despite wake-sleep cycle disruptions caused for example by night work or jet-lag.[8,53] With and without prophylactic naps,[5] SR caffeine may be advisable for all sleep deprivation conditions, particularly within the context of a sustained operation.[2,54]

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